

Remarks

Claims 1 to 25, 28 to 33 and 35 to 40 are pending in the current application.

35 USC §102(b) rejection

On page 3, the Office rejected claim 24 under 35 USC 102(b) as being anticipated by Greenberg (US Patent No. 5,569,458 hereafter "Greenberg"). Greenberg is said to disclose a dietary supplement comprising bromelain, papain, trypsin, and chymotrypsin, vitamins, selenium containing substances, citrus bioflavonoid complex, amino acids, and mucopolysaccharides. With a reference to col. 5, lines 26 to 28, Greenberg is also said to disclose a composition that strengthens the immune system.

Claim 24 is directed to a food product for food supplementation.

The Office, in response to applicant's argument that Greenberg teaches that his composition is encapsulated, expressed the opinion that encapsulating the composition comprising of powder ingredients as taught by Greenberg does not result in a structural difference between the claimed invention and the prior art composition.

Applicant submits that the encapsulation renders Greenberg's product inappropriate as a "food product for food supplementation."

Applicant also notes that Greenberg discloses in col. 5, lines 26 to 28 that goldenseal generally strengthens the immune system. However, the presently claimed invention requires the *food product* to strengthen the immune system. Goldenseal is not recited in the claims or mentioned in the specification.

35 USC §103(a) rejection

Starting on page 4, the Office rejected claims 1-23, 25, 28-33 and 35-40 under 35 USC 103(a) as being unpatentable over Greenberg in view of Murray, MT (2001, Proteolytic enzymes in Cancer Therapy, pages 1-2 hereafter "Murray"), and further in view of Manthey et al (Current Medicinal Chemistry, 2001, Vol. 8, p. 135-153 hereafter "Manthey"), and further in view of Rayman (previously cited, The Lancet, 2000, Vol. 356, p. 233-241 hereafter "Rayman"), and further in view of Vetvicka et al (JANA, 2002, Vol. 5, No. 2, p. 5-9 hereafter "Vetvicka"), and further in view of Ochao et al (Journal of Parenteral & Enteral Nutrition, 2001, Vol. 25, No. 1, p. 23-29 hereafter "Ochao"), and further in view of Birt et al (Pharmacology & Therapeutics, 2001, Vol. 90, p. 157-177 hereafter "Birt"), and further in view of Jensen et al (J. Nutr. 1999, Vol. 129, p. 1355-1360 hereafter "Jensen").

The Office's argument

Greenberg is said to teach a composition comprising plant/animal proteases, vitamin A, C and E, selenium amino acid complexes (69.2 mg) and bioflavonoid complex (36.4 mg). Greenberg is also said to teach that the composition strengthens the immune system (col. 5, 26 to 28).

The Office acknowledges that Greenberg does not teach one or more proteases having a total concentration of 20% to 60% by weight of active constituents in the composition, and flavonoids having a total concentration of 10% to 50% by weight of active constituents.

However, Murray is said to teach a composition comprising 47.4% pancreatin, 28.5% papain, and 12% bromelain. Murray is also said to teach that because the animal and vegetarian-derived enzymes have slightly different effects using the combination of the enzymes would provide maximum benefit.

Moreover, Manthey Manthey is said to teach anti-inflammatory properties of a composition comprising 10% of a flavonoid, due to inhibition of the synthesis of pro-inflammatory mediators of immune and inflammatory responses.

Rayman is said to teach supplementation of selenium as sodium selenite, and that supplementation of 200 µg selenium per day has immunoenhancing effects and additionally cells of the immune system may have an important functional need for selenium.

The Office also refers MPEP §2144.05 and *In re Aller* noted therein in which the court concluded that, if certain conditions are met, the discovery of the optimum or workable ranges is not inventive.

Vetvicka is cited for its teaching of β-glucans that are said to exhibit immunostimulating properties, including antibacterial and anti-tumor activities. Vetvicka teaching is said to provide preclinical evidence for the beneficial effects of orally-administered β-glucans. The Office concluded that therefore a person of ordinary skill in the art could have been motivated to use polysaccharide β-glucan in an immunoenhancing composition.

Ochao is cited for its teaching of dietary L-arginine that is said to enhance and stimulate cellular immune response. The Office concluded that therefore a person of ordinary skill in the art would have been motivated to use L-arginine in an immunoenhancing composition.

For further motivation to use flavonoid quercetin from onion, the Office cites in Birt who teaches flavonoids have many biological properties including the ability to regulate and

enhance host immune function. Birt is further said to teach that studies show that the adsorption of quercetin is 3 fold greater after ingestion of quercetin predominantly in the glycosodic form from onions.

Finally, the Office cited Jensen for further motivation to use the antioxidant vitamin E acetate instead of vitamin E succinate as taught by Greenberg, as Jensen teaches that vitamin E acetate is a better vitamin E source because of higher efficiency of absorption.

The Office expressed the opinion that a person of ordinary skill in the art at the time the invention was made, *could* have been motivated to modify the concentration of animal and/or plant proteases and flavonoids in the compositions as taught by Greenberg according to Murray and Manthey with predictable results of providing a composition with improved immune strengthening properties.

Moreover, the Office expressed the opinion that the person of ordinary skill in the art at the time the invention was made *could* have been motivated to use the teaching of Rayman and use selenium as sodium selenite in the composition of Greenberg with predictable results of providing a composition with improved immune strengthening properties. The Office further stated that, in view of the teachings of Rayman, the claim composition would have been obvious because substitution of one known form of selenium, in this case sodium selenite, for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The Office refers to Jensen for the substitution of Greenberg's vitamin E succinate with vitamin E acetate and Vetvicka, Ochao and Brit for the specific teaching discussed above.

The Office cited immunostimulating and antioxidant properties and immunoenhancing

properties of different members of the claimed composition as motivators for combining the references to arrive at the present invention.

The Office further cited KSR stating that a combination which only unites old elements and does no more than yield predictable results is obvious.

Applicant's argument

Applicant concurs with the Office in that Greenberg notes that his digestive enzymes should not be present in his formulation in a weight percentile of more than 10%. Greenberg states that the digestive enzymes aid and increase absorption of the remaining nutrients. Greenberg includes goldenseal into his composition to prevent the digestive enzymes from "eating up" the other nutrients (col. 3, lines 59 to 66). With the inclusion of the digestive enzymes, Greenberg seeks to remedy a common dietary supplement problem of low absorbability of the nutrients (col. 4, lines 45 to 48). Greenberg also notes, that although the addition of enzymes may not increase its long-term marketability [due to shorter shelf life], the formula's increased absorbability of its nutrients greatly increases the effectivity and performance of his invention (paragraph bridging col. 4 and 5).

Thus, it is clear that Greenberg includes digestive enzymes for their effect on absorbability. However, Greenberg includes the digestive enzymes only over reservations of the effect of these enzymes on shelf life and on the other ingredients of his formulation.

Murray reports on the use of proteolytic enzymes in cancer therapy. Murray teaches that proteolytic enzymes can be used along with conventional cancer treatments such as chemotherapy or radiation. However, Murray does not refer to any of the ingredients

of Greenberg. Murray reports on ZYMACTIVE that contains three proteolytic enzymes amounting, according to the Office's calculation, to almost 90% of the total composition, namely 47.4%, 28.5% and 12% (pancreatin, papain and bromelain), while the remainder is made up by peptizyme SP.

Manthey expands on the underlying mechanisms that are thought to be responsible for anti-inflammatory and anti-cancer actions of certain citrus flavonoids. His findings are based on compositions primarily containing flavonoids and analogues thereof. The passage the Office refers to to support that Manthey discloses 10% flavonoids describes a mixture of the citrus flavonoid hesperidine and its flavone analog, diosmin. The action of the flavonoids are said to be mediated by the inhibition of a wide variety of enzymes in the body which is described to be a key to their advantageous properties.

Rayman's review article discusses the importance of selenium to human health. Different forms of selenium are discussed as well as sources and the bioavailability of selenium. The focus of the review is on selenium source by itself. Interactions with other nutrients are not considered.

Applicants respectfully submit that Greenberg's expressed reservation about the inclusion of digestive enzymes into his composition, in particular, his clearly expressed concern that these digestive enzymes might "eat up" (col. 3, lines 63) the other nutrients in his composition would hardly motivate the person skilled in the art to add more digestive enzyme, such as the claimed total concentration of 20% to 60% by weight of active constituents of plant/animal proteases into Greenberg's composition that does indeed contain other nutrients.

The other art cited by the Office does not help in overcoming Greenberg's reservations.

While Murray reports on the proteolytic enzymes in cancer therapy at high concentrations none of the other ingredients of Greenberg's composition nor any effects that the proteolytic enzymes might have on them are mentioned by Murray.

With regard to flavonoid containing substances, Greenberg notes that these are included in his composition to enhance absorption of vitamin C (col. 6, lines 6 to 8). Manthey reports on underlying mechanism of effects of flavonoids, namely their anti-inflammatory and anti-cancer actions through the induction of hepatic phase I and II enzymes (see abstract). Vitamin C uptake is apparently of no concern.

Thus, applicant respectfully submits that the rationale of *In re Aller* does not apply in this case. It is well known that particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (see MPEP 2144.05). Providing weight percentiles of flavonoids as currently claims (10% to 50%) goes far beyond the optimization of ranges contemplated by the court of *In re Aller*.

Rayman's review article notes the differences between the less available selenomethionine and the more readily available selenites and selenates. Rayman points out that the organic forms have the advantage of being less acutely toxic, while they may be more toxic during long term use. This leaves selenites and selenates as more acutely toxic alternatives with less disadvantageous long term effects.

Rayman leaves open which option might be preferable. Considering selenium by itself,

Rayman does not discuss or even consider the effects on other nutrients in a composition such as the one taught by Greenberg.

In view of the above, applicant submits that the Office has not shown that the combination of the references cited by the Office provide the claimed invention with the level of predictability required to support a *prima facie* case of obviousness. In fact, the primary reference, namely Greenberg, expressed not only reservations about the use of digestive enzymes but also uses flavonoids for a purpose that put them outside the realm of *In re Aller*.

Applicants have clearly shown that no *prima facie* case of obvious has been established with regard to claims 1 to 23, 25, 28 to 33 and 35 to 40 and that claim 24 is not anticipated by Greenberg. In view of this, an early issuance of a notice of allowance is respectfully requested.

The Commissioner is authorized to charge any fee deficiencies or overpayment to the undersign's deposit account 50-3135.

Respectfully submitted,

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